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(54) Title: METHOD FOR THE TREATMENT OF FERTILITY DISORDERS

(57) Abstract

In the method of therapeutic management of infertility by intrauterine insemination the improvement consisting of a) the dose–dependent suppression of endogenous gonadotropins, especially LH, with a LH–RH Antagonist allowing the maintenance of physiological oestrogen levels, b) exogeneous stimulation of the ovarian follicle growth, c) ovulation induction with HCG, native LHRH, LHRH–Agonists or recombinant LH, d) intrauterine insemination by sperm injection. The LHRH Antagonists may be preferably Cetrorelix or Antarelix. The stimulation is performed by administration of HMG or recombinant FSH with or without recombinant LH or with antiestrogens as for example Chlomiphen as well as with the combination of antiestrogens as for example Chlomiphen with gonadotropins.

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Method for the treatment of fertility disorders

One of the ethical problems of more recent times is the increasing sterility and unwanted childlessness of many couples. With respect to the therapy of these fertility disorders, inter alia, the following treatment methods of artificial fertilization have been established:

1. Substitution therapy - applied in patients with hypogonadotropic amenorrhoea
2. Stimulation therapy - given to anovulatory patients with active, albeit deranged hypothalamic pituitary-ovarian axis
3. Regulation therapy - employed in women with POCD
4. Hyperstimulation therapy - used in IVF, gamete intrafallopian transfer (GIFT), tubal embryo transfer (TET), intracytoplasmatic sperm injection (ICSI) and intrauterine insemination (IUI).

The present invention especially relates to the improvement of the method of artificial sperm cell transfer in the uterus, i.e. the fertilization by intrauterine insemination (IUI) mentioned under item 4.

For the methods under items 2 and 4, it is necessary to stimulate follicle growth, which is achieved by the administration of gonadotropins, e.g. HMG, FSH and LH, with or without preliminary therapy with clomiphene.
It has further proved that the risk of luteinization by a premature LH surge, which leads to unfavourable implantation conditions and relatively low pregnancy rates, can be decreased by complete suppression of the endogenous gonadotropins using GnRH agonists (Garcia et al., 1984; Navot et al., 1991; Hoffmann et al., 1993).

For the control of ovarian stimulation with subsequent induction of ovulation, with the aim of obtaining fertilizable egg cells, both recombinant FSH and HMG and FSH and HMG obtained from urine are employed.

In connection with IUI, it is also desirable to control follicle growth and to specifically trigger ovulation.

The statements in the specialist literature about the therapeutic accompaniment of IUI, in particular using GnRH analogues, are mainly negative, such as, for example, the following:

1. IUI after ovarian stimulation with clomiphene may be important as the 1st choice of therapy, provided the male partner has a normal spermiogram (Hum. Reprod. 1997; July; 12(7):1458-1463).
2. GnRH agonists/HMG stimulation, however, may be ineffective in routine IUI. Treatment with GnRH agonists with maximum suppression of the endogenous gonadotropins requires a relatively long treatment period (about 3 weeks) and leads to an increased consumption of HMG and is associated with side effects.
3. Reports also exist which confirm that an increase in the pregnancy rate is not achieved by the use of GnRH agonists/HMG against HMG alone for IUI treatment in the case of unclarified infertility (Hum. Reprod. 1994 June 9(6) 1043-1047.
4. The cost differences of GnRH-a/HMG stimulation compared with clomiphene/HMG is indicated by Finnish authors in Eur. J. Obstet. Gynecol. Reprod. Biol. 1997 July 74: GnRH-a/HMG stimulation is not cost-effective in routine IUI therapy.

In a study by Diedrich et al. from 1994 Hum. Reprod. 1994 May; 9(5), the suppression of the undesired, premature LH surge by cetrorelix during ovarian stimulation with HMG and the on-time induction of ovulation was described in the context of a COS-ART study.

It was possible to shorten the length of the treatment period using this LHRH antagonist and the partial dose-dependent suppression of the endogenous gonadotropins additionally proved advantageous, since it was possible

to reduce the consumption in comparison to the use of agonists of HMG.

The object of the invention is therefore to improve, i.e. to make inexpensive and more effective, the treatment method of intrauterine insemination known per se and thus in the end to fulfil the desire for children of many couples.

It has now been found that the treatment method of IUI can be improved by carrying out a partial suppression of the endogenous gonadotropins, which can only be achieved by means of LHRH antagonists, preferably cetrorelix or antarelix. At the same time, follicle growth is stimulated by means of urinary or recombinant FSH, HMG or clomiphene, or a combination thereof. Subsequently, ovulation can be triggered at a desired time by means of HCG, native LHRH, LHRH agonists or recombinant LH. Surprisingly, this takes place when the dominant follicle has reached a diameter of about 16-18 mm. Intrauterine sperm injection then takes place with the aim of intracorporeal fertilization. It is possible in this way to carry out a stimulation treatment which is less stressful for the patient and guarantees a high degree of safety with respect to the ovulation time and leads to a saving in cost.

Claims:

1. In the method of therapeutic management of infertility by intrauterine insemination, the improvement consisting of
   a) the dose-dependent suppression of endogenous gonadotropins, especially LH, with an LH-RH antagonist allowing the maintenance of physiological oestrogen levels
   b) exogenous stimulation of the ovarian follicle growth
   c) ovulation induction with HCG, native LHRH, LHRH agonists or recombinant LH.
   d) intrauterine insemination by sperm injection.

2. The method of therapeutic management of infertility by intrauterine insemination according to claim 1 in which the LHRH antagonist is cetrorelix.

3. The method of therapeutic management of infertility by intrauterine insemination according to claim 1 in which the LHRH antagonist is antarelix.

4. The method of therapeutic management of infertility by intrauterine insemination according to claim 1 in which the stimulation is performed by administration of urinary or recombinant FSH or HMG, with or without recombinant LH.

5. The method of therapeutic management of infertility by intrauterine insemination according to claim 1 in which the ovarian stimulation is achieved with antioestrogens as for example clomiphene.

6. The method of therapeutic management of infertility by intrauterine insemination according

to claim 1 in which the ovarian stimulation is achieved with the combination of antioestrogens as for example clomiphene with gonadotropins.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 99/02133

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/09 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 611 572 A (ASTA MEDICA AG) 24 August 1994 (1994-08-24) *cf. abstract and page 3, lines 47-52, page 4, lines 15-21* ---	1-6
Y	EP 0 788 799 A (ASTA MEDICA AG) 13 August 1997 (1997-08-13) *cf. abstract, col. 1, lines 11-14, 39-54, col. 2, lines 40-43* ---	1-6
Y	DE 196 04 231 A (SCHERING AG) 31 July 1997 (1997-07-31) *cf. abstract, col. 1, first para., col. 2, lines 15-28* ---	1-6
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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 August 1999	31/08/1999

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BOUCHARD P., ET AL. : " Endocrine features of combined gonadotropin and GNRH antagonist ovulation induction" OVUL. IND. UPDATE '98, PROC. WORLD CONF., 2ND, 1998,1997, pages 115-119, XP002111491 *cf. introduction*	1-6
A	US 5 130 137 A (CROWLEY JR WILLIAM F) 14 July 1992 (1992-07-14) *cf. col. 2, last para. bridging with col. 3, lines 1-7*	1-6

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0611572 A	24-08-1994	DE 4305225 A	25-08-1994
		AU 671881 B	12-09-1996
		AU 5523594 A	25-08-1994
		BR 9400617 A	27-09-1994
		CA 2115943 A	20-08-1994
		CN 1112019 A	22-11-1995
		CZ 9400312 A	14-09-1994
		FI 940779 A	20-08-1994
		HR 940117 A	31-08-1996
		HU 67117 A	28-02-1995
		JP 6271476 A	27-09-1994
		MX 9401312 A	31-08-1994
		NO 940564 A	22-08-1994
		NZ 250906 A	27-07-1997
		NZ 314707 A	25-02-1999
		SG 46632 A	20-02-1998
		SI 9400087 A	31-12-1994
		SK 19594 A	07-09-1994
		ZA 9401136 A	29-08-1994
EP 0788799 A	13-08-1997	JP 9227404 A	02-09-1997
DE 19604231 A	31-07-1997	AU 1596997 A	22-08-1997
		CN 1209750 A	03-03-1999
		CZ 9802391 A	11-11-1998
		WO 9727863 A	07-08-1997
		EP 0877621 A	18-11-1998
		NO 983465 A	18-09-1998
		PL 328066 A	04-01-1999
US 5130137 A	14-07-1992	AU 6353790 A	11-03-1991
		WO 9101748 A	21-02-1991

INTERNATIONALER RECHERCHENBERICHT

Inte. ..ionales Aktenzeichen
PCT/EP 99/02133

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K38/09 A61K31/135

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Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	EP 0 611 572 A (ASTA MEDICA AG) 24. August 1994 (1994-08-24) Zusammenfassung und Seite 3, Zeilen 47-52, Seite 4, Zeilen 15-21.	1-6
Y	EP 0 788 799 A (ASTA MEDICA AG) 13. August 1997 (1997-08-13) Zusammenfassung, Spalte 1, Zeilen 11-14, 39-54, Spalte 2, Zeilen 40-43.	1-6
Y	DE 196 04 231 A (SCHERING AG) 31. Juli 1997 (1997-07-31) Zusammenfassung, Spalte 1, erster Abschnitt, Spalte 2, Zeilen 15-28.	1-6

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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	BOUCHARD P., ET AL. : " Endocrine features of combined gonadotropin and GNRH antagonist ovulation induction" OVUL. IND. UPDATE '98, PROC. WORLD CONF., 2ND, 1998,1997, Seiten 115-119, XP002111491 Einführung. ---	1-6
A	US 5 130 137 A (CROWLEY JR WILLIAM F) 14. Juli 1992 (1992-07-14) Spalte 2, letzter Abschnitt "bridging with col 3" Zeilen 1-7. _____	1-6

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Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 0611572 A	24-08-1994	DE 4305225 A	25-08-1994
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		AU 5523594 A	25-08-1994
		BR 9400617 A	27-09-1994
		CA 2115943 A	20-08-1994
		CN 1112019 A	22-11-1995
		CZ 9400312 A	14-09-1994
		FI 940779 A	20-08-1994
		HR 940117 A	31-08-1996
		HU 67117 A	28-02-1995
		JP 6271476 A	27-09-1994
		MX 9401312 A	31-08-1994
		NO 940564 A	22-08-1994
		NZ 250906 A	27-07-1997
		NZ 314707 A	25-02-1999
		SG 46632 A	20-02-1998
		SI 9400087 A	31-12-1994
		SK 19594 A	07-09-1994
		ZA 9401136 A	29-08-1994
EP 0788799 A	13-08-1997	JP 9227404 A	02-09-1997
DE 19604231 A	31-07-1997	AU 1596997 A	22-08-1997
		CN 1209750 A	03-03-1999
		CZ 9802391 A	11-11-1998
		WO 9727863 A	07-08-1997
		EP 0877621 A	18-11-1998
		NO 983465 A	18-09-1998
		PL 328066 A	04-01-1999
US 5130137 A	14-07-1992	AU 6353790 A	11-03-1991
		WO 9101748 A	21-02-1991